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The roles of bun/d-dimer and bun/lactate ratios in indicating mortality in intensive care patients with COVID-19

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Abstract

Aim: Coronavirus disease 2019 (COVID-19) is an epidemic disease with variable symptoms and high mortality rates. Therefore, patient follow-up is very significant. We aimed to investigate whether blood urea nitrogen (BUN), D-dimer and lactate parameters, which are laboratory tests used in follow-up, predict mortality.

Material and Methods: The study included 173 COVID-19 patients hospitalized in the pandemic intensive care unit from March 2020 to June 2020. We retrospectively recorded patient age, gender, comorbidity, radiological involvement, oxygen demand, APACHE scores, in-hospital mortality status, BUN, lactate, and D-dimer levels, BUN/D-dimer ratio (BDR), BUN/lactate ratio (BLR). Then we made the statistical comparison between the groups by grouping the patients as discharged and deceased.

Results: Among the patients included in the study, 107 (61.8%) were male and 66 (38.2%) were female. The mean ages between those discharged and those who died in the hospital were 73 and 67.5 years, respectively, and there was a statistically significant difference. The median BUN, d-dimer, lactate and BDR, BLR values of the patients in the non-survivor group were significantly higher than those in the survivor group. BLR had the highest diagnostic ratio (25.03) for estimating in-hospital COVID-19 mortality.

Discussion: We found that BUN, BDR, and BLR levels were reliable predictors of in-hospital mortality in COVID-19 patients. However, BLR was a potent risk assessment tool, especially in defining the risk of in-hospital death.

Keywords

COVID-19, Lactate, Blood Urea Nitrogen, D-Dimer, Mortality

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Introduction

In Wuhan, China, there has been an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since December 2019 [1]. Although COVID-19 is primarily a respiratory disease, it can affect multiple organ systems, including the gastrointestinal, hepatic, cardiac, neurological, and renal systems. Therefore, patient follow-up is significantly substantial.

SARS-CoV-2 infection induces a profound inflammatory response that triggers the coagulation cascade. Activation of the coagulation cascade in COVID-19 patients is associated with adverse clinical outcomes, including hypercoagulation status and death. Thrombotic complications and coagulopathies, including disseminated intravascular coagulopathy, are common in COVID-19 and reflect activation of the coagulation cascade, possibly due to viremia or cytokine storm, or possibly superinfection and organ dysfunction. D-dimer is considered the best available laboratory diagnostic marker for hemostatic abnormalities associated with COVID19 [2]. D-dimer is a fibrin degradation product widely used as a biomarker for thrombotic disorders. A D-dimer value of less than 0.5 µg/mL is generally considered normal, and values increase with age and pregnancy. The D-dimer level rises as the severity of community-acquired pneumonia increases. Following the outbreak of the COVID-19 pandemic, D-dimer has been identified as a potential indicator for the prognosis in COVID-19 patients. Elevated D-dimer levels at presentation and significantly increased D-dimer levels (3 to 4 fold) over time are associated with higher mortality, possibly reflecting activation of coagulation from infection/sepsis, cytokine storm, and impending organ failure [3]. There were many studies about the relationship between D-dimer levels and mortality in COVID-19 patients. Although guidelines proposed serial D-dimer measurement for COVID-19 patients, the optimal limit for D-dimer has not yet been determined.

Blood urea nitrogen (BUN) is a nitrogenous end product of protein metabolism and is associated with death in various diseases. BUN represents a surrogate marker to predict persistent organ failure 48 hours after hospital admission in addition to its role in the prediction of kidney function [4]. A multicenter study reported that BUN independently predicted mortality in critically ill patients admitted to the intensive care unit (ICU) [5]. Activation of neurohumoral factors, including the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAS), and arginine vasopressin (AVP), increases flow-dependent urea absorption in the proximal and distal tubules. Elevated blood urea nitrogen (BUN) level can be considered a surrogate marker for neurohumoral activation in heart failure patients [6]. In addition, hyperlactatemia developing with increased hypoxia has traditionally been associated with poor outcomes in critically ill patients, and lactate value is considered one of the most important biomarkers of disease severity in patients with sepsis [7].

Although death rates from COVID-19 are around 2% worldwide, according to the WHO data, some publications report that mortality rates are much higher in patients admitted to the emergency department. This situation may be due to uncertainties and delays in diagnosis and appropriate treatment of the disease. There is a need for an accessible biomarker or calculations that can predict the mortality of COVID-19 patients. In this study, we aimed to investigate the roles of Bun/D-Dımer and Bun/Lactate Ratios, which are laboratory tests used in the follow-up of COVID-19 patients, in predicting mortality.

Material and Methods

The Ethical Committee and the Institutional Review Board of Usak University Faculty of Medicine, where the study was conducted, approved the study design. We reviewed the medical records of 173 patients hospitalized in the pandemic intensive care unit between March-June 2020. We retrospectively analyzed the patient files, and we recorded the APACHE scores, BUN level, lactate, BUN/lactate ratio, D-dimer, BUN/d-dimer ratio, radiological involvement level and age, gender, comorbidity (additional diseases), oxygen requirement, and in-hospital mortality situations of patients. All data were received over the hospital communication system. We made a statistical comparison between the groups by grouping the patients as discharged and deceased using SPSS 20 SPSS 20.0 package program (SPSS Inc., Chicago, IL). We conducted the normality analyses of the data using histograms and the Kolmogorov–Smirnov test. While the normally distributed quantitative data were expressed as mean ± standard deviation values, the non-normally distributed quantitative data were expressed as median values (25–75% quartiles). Categorical variables were expressed as frequency (percentage) values. We investigated the differences between the groups using the Mann–Whitney U test for the non-normally distributed quantitative variables. Intragroup comparisons of the categorical variables were made using the chi-square test. Receiver operating characteristic (ROC) analysis was performed for determining the non-survivor mortality predictive power of the biochemical parameters. The optimum cut-off levels of the biochemical parameters were determined using Youden's index (sensitivity +1 − specificity). We calculated the sensitivity, specificity, and positive and negative predictive values of the parameters for the optimum cut-off levels. A value of $p<0,05$ was accepted as statistically significant.

Results

We obtained the patients' Acute Physiologic and Chronic Health Evaluation (APACHE II) scores by using the patients' consciousness status, chronic disease status, vital status, and laboratory parameters in the first 24 hours. Results were significantly higher in the non-survivor group than in the survivor group.

Table 2 shows the comorbidity presence in the survivor and non-survivor groups. We compared the frequencies with the chi-squared test. Although the presence of comorbidity was generally significantly higher in the non-survivor group, there was no significant difference in terms of the type of comorbidities (Table 1).

Table 2 shows the rates calculated with the biochemistry parameters measured within the groups using the Mann-Whitney U test. Accordingly, the median BUN, d-dimer, lactate and BDR, and BLR values of the patients in the survivor group were significantly higher than those in the survivor group.

Here, the cut-off value is calculated to indicate mortality, and

the specificity and sensitivities were determined according to these cut-offs showed in Table 3. Accordingly, we found the BUN/lactate ratio with the lowest sensitivity and the highest specificity and positive predictive value and the BUN/d-dimer rate with the maximum sensitivity.

If we look at the likelihood ratios, the analyzed parameters are strong indicators that the risk of mortality exists (rule in, LR>1). However, they are not very strong indicators that it does not exist (rule out, LR<1). Diagnostic accuracy rates are between 60-70%, and we observe the highest BUN. The odds ratio is the ratio of occurrence to the absence of events. We found +LR to be the highest in the lactate test and the most helpful parameter in demonstrating mortality risk. Positive Youden indices in all parameters indicate the usability of all of them diagnostically, but the BUN test is the best indicator (Table 3).

If the sensitivity (true positive rate) was plotted against the false positive rate (1-Specificity), the resulting curves are called ROC curves (Receiver Operating Curve).

There is FPR (False Positive Rate) on the X-axis and TPR (True Positive Rate) on the Y-axis in the ROC curve. The higher the level under the curve, the higher the discrimination performance between classes. In estimating in-hospital COVID-19 mortality, the area under the curve (AUC) for BUN was the highest (0.74), and the diagnostic odds ratio was the highest for BLR (25.03) (Figure1).

Table 1. General demographic characteristics, mortality, comorbid disease, pulmonary involvement rates, and ventilation type at the time of hospitalization of the patients. a Data are presented as median (%25-%75), b Data are presented as n (%)

Variables	Non-survivor (83)	Survivor (90)	p value
Agea	73 (64-81)	67.5 (56.75-76)	0.007
Genderb			
Male	51 (%61.4)	56 (%62.2)	0.916
Female	32 (%38.6)	34 (%37.8)	
PCRb			
Negative	42 (%66.7)	54 (%87.1)	0.007
Positive	21 (%33.3)	8 (%12.9)	
Radiological İnvolvementb			
Typical	54 (67.5%)	52 (58.4%)	0.223
Atypical	26 (32.5%)	37 (41.6%)	
Level b			
Mild	26 (32.5%)	51 (57.3%)	0.010
Severe	54 (67.5%)	38 (42.7%)	
APACHE Scorea	21,5 (12-32)	16 (12-23.5)	0.014
Ventilationb			
Non-invasive	63 (76.8%)	83 (92.2%)	0.005
İnvasive (intubation)	19 (23.2%)	7 (7.8%)	
Comorbid diseaseb			
Without	26 (%40)	39 (%60)	0.000
With	58 (%60)	51 (%40)	0.000
Type of comorbidityb Diabetes Mellitus			
Yes	20 (%24.1)	17 (%18.9)	0.404
No	63 (%75.9)	73 (%81.1)	
Hypertension			
Yes	19 (%22.9)	14 (%15.6)	0.220
No	64 (%77.1)	76 (%84.4)	
Chronic Obstructive Pulmonary Disease			
Yes	18 (%21.7)	25 (%27.8)	0.354
No	65 (%78.3)	65 (%72.2)	
Coroner Arter Disease			
Yes	20 (%24.1)	15 (%16.7)	0.224
No	63 (%75.9)	75 (%83.3)	
Chronic Renal Failure			
Yes	4 (%4.8)	4 (%4.4)	0.907
No	79 (%95.2)	86 (%95.6)	
Malignancy			
Yes	7 (8.4%)	5 (5.6%)	0.457
No	76 (91.6%)	85 (94.4%)	
Cerebrovascular disease			
Yes	3 (3.6%)	3 (3.3%)	0.920
No	80 (96.4%)	87 (96.7%)	

Discussion

In the study, we showed the power of BUN, lactate, D-dimer, BDR, and BLR ratios in predicting mortality in COVID-19 patients hospitalized in the intensive care unit.

While making parameter selections, we considered the importance of hypoxia in clinical worsening by prioritizing the lung and vascular endothelium, which are the tissues most affected by COVID-19.

There are many studies conducted separately for the BUN test in the CURB-65 scoring system used in the estimation of hospitalization and mortality in the presence of pneumonia [8]; the D-dimer test, is used to exclude thromboembolism and is

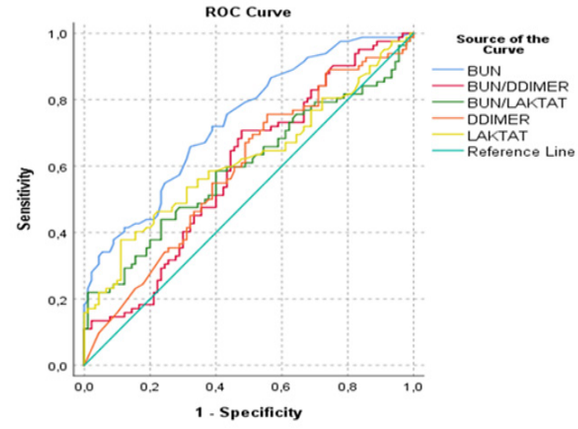

Figure 1. ROC curve by non-survivor group mortality

Table 2. The biochemical values of the parameters and the ratios of the calculated parameters belonging to the study groups, data are presented as median (%25-%75)

	Non-survivor (83)	Survivor (90)	p value
BUN	38 (25-60)	23 (14-34.25)	0.000
D-dimer	2430 (1401-4300)	1710 (965.25-4204.75)	0.029
Lactate	1.81 (1.29-2.73)	1,56 (1.19-1.9)	0.008
BUN/D-dimer	0.0164 (0.0091-0.0299)	0,0118 (0.0066-0.0262)	0.038
BUN/Lactate	19.24 (10.38-30.99)	14,15 (8.79-22.92)	0.029

Table 3. ROC Analysis result by in-hospital mortality status and Odds ratio results obtained according to optimum cut off values. CI: Confidence interval; AUC: Area under the curve.

	BUN	D-DIMER	LACTATE	BUN/LACTATE	BUN/D-DIMER
AUC (95%CI)	0.735 (0.662-0.809)	0.592 (0.506-0.677)	0.618 (0.532-0.703)	0.592 (0.507-0.678)	0.597 (0.510-0.683)
Std Error	0.037	0.043	0.044	0.043	0.044
p value	0.000	0.035	0.007	0.033	0.029
Cut off level	>30.5	>1397.5	>2.26	>0.012	>41.101
Sensitivity	66.27%	75.90%	37.80%	71.08	21.95%
Specificity	67.78%	44.44%	88.89%	51.11%	98.89%
Positive predictive value (PPV)	65.48%	55.75%	75.61%	57.28%	94.74%
Negative predictive value (NPV)	68.54%	66.67%	61.07%	65.71%	58.17%
Likelihood ratio for positive test	2.06	1.37	3.40	1.45	19.76
Likelihood ratio for negative test	0.50	0.54	0.70	0.57	0.79
Diagnostic odds ratio	4.13	2.52	4.86	2.57	25.03
Diagnostic effectiveness (accuracy)	67.05%	59.54%	64.53%	60.69%	62.21%
Youden's index	0.340	0.203	0.267	0.222	0.208

a prognostic indicator in community-acquired pneumonia [9], and the lactate test, is a prognostic indicator as a product of anaerobic glycolysis [10]. In addition to these studies that show their significance by evaluating individual parameters, our study aims to show the correlation between BLR and BDR levels and in-hospital mortality. However, this study is unique for the simultaneous comparison of these three parameters for mortality estimation. It will contribute to the literature to find an assessment tool with a high diagnostic value that can predict the mortality rate of COVID-19 patients.

In this study, the levels of all parameters looked at were significantly higher in the non-survivor group than in the survivor group. We calculated cut-off values to determine mortality. When lactate exceeded the level of 2.26, it had a high specificity as an indicator of mortality. We showed that mortality increased four times for lactate values above 2.26 mmol/L in the study. Lactate is an established prognostic indicator in critical care. However, extensive additional studies are needed. COVID-19 can be considered a form of sepsis. With this approach, the first Update to the "Surviving Sepsis Campaign Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU" recommends the use of serum lactate measurement to assess fluid therapy response in adults with COVID-19 and shock [11]. In a study of 235 patients, Kayina et al. showed that survivors had higher baseline serum lactate levels [12]. These results are similar to our findings. Also, a retrospective study of 553 patients by Jo et al. showed that baseline serum lactate levels were equivalent to established pneumonia scoring, such as CURB65, which is used to predict the prognosis of patients with community-acquired pneumonia [13]. This research also shows a correlation between BUN levels and lactate levels. Gwak et al. conducted a study with the data from 397 hospitalized patients, 18% of whom admitted to the intensive care unit, and they found an independent association between patients' initial serum lactate concentration and in-hospital mortality [14]. But these studies did not evaluate the BLR in-hospital mortality. Our study is the first study that shows the correlation between BLR and in-mortality. In addition, the BUN/lactate ratio increased 25 times, which is very significant in our study. We know that BUN is a prominent indicator in end-stage heart, kidney disease, and some life-threatening diseases. In a search conducted with 383 elderly veterans, elevated BUN level was an indicator of the severity of acute and chronic diseases. In addition, BUN ≥ 30 mg / dL detected in the Cox PH model (a model where the danger of one individual is assumed to be proportional to the risk of another individual) was associated with an approximately 2-fold increased risk of mortality [15]. According to many studies, a high BUN level is an indicator of the severity of pneumonia [16]. According to ROC analysis performed to predict in-hospital mortality, BUN levels reached 0.74 AUC in our study. A BUN level above 30.5 mg/dl had an odds ratio of 4.13 in predicting in-hospital mortality of COVID-19 patients. In other words, the mortality rate increased four times at BUN values above 30.5 mg/dL.

D-dimer test, the last parameter we examined, was also significantly higher in the non-survivor group. However, the specificity and sensitivity of the cut-off value we calculated to determine the mortality risk were not significant. These results were similar to a retrospective study of 1065 hospitalized patients in the United States. Navmagon L et al. found that every 1 µg/ml increase in admission D-dimer was associated with a hazard ratio of 1.06 (95% CI 1.04–1.08, p<0.001) for all-cause mortality. However, they found D-dimer to be a poor prognostic test for predicting mortality, with an area under the curve of ROC curves for the D-dimer trend being just 0.67 [17]. Another meta-analysis study done by Gungor et al. showed that patients with elevated D-dimer on admission had a higher risk of mortality (relative risk, RR 1.82) and disease severity (RR 1.58) compared to the patients with normal levels of D-dimer [18]. In Poudel et al.'s study, a higher D-dimer value on hospital admission was significantly associated with in-hospital mortality in patients with COVID-19. D-dimer is a fibrin degradation product, and its primary utility is in the diagnosis and management of thrombotic disorders [3]. Cheng A et al found that the predictive effect of BUN combined with D-dimer had significantly better AUC values than that of the BUN or D-dimer alone, but when we examined the BUN to d-dimer ratio [19], there was no significant differences between the two

groups for diagnostic risk determination.

Also, this study had some limitations. The initial values of the patients in the intensive care unit were included in the study, but no comparison could be made with the first admission. In addition, the fact that the treatment protocols we received during COVID-19 were not evaluated in this study was another limitation of the study. Lastly, the fact that this study was a single-center study was likewise a limitation.

In conclusion, accurate and widely available biomarkers may be prognostic and utilized to manage COVID-19 disease. Accordingly, we found that BUN, D-dimer, lactate, BLR, and BUN BDR levels are reliable predictors of in-hospital mortality in patients with COVID-19. Still, the BUN test is the most powerful in showing the risk of in-hospital mortality, while BLR is a powerful assessment tool as a clinical criterion in mortality estimation.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no conflicts of interest.

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